REMARKS

Reconsideration of the rejections set forth in the Office action mailed December 11, 2000 is respectfully requested. Claims 17-21, 23, and 56-58 are currently under examination; claims 59-62 are added by the present amendment.

I. Amendments

The specification has been amended to add a statement of Government support of the invention.

Claims 17 and 57 have been amended, to expedite allowance, to incorporate the subject matter of claim 23; that is, to state that the binding group Cy_N is a heteroaryl group. Support is found in original claim 23 and in the specification at page 4, line 6.

In the specification and the enclosed Declaration under 37 CFR §1.132, six examples of N-heterocyclic aromatic rings are shown to be effective as binding groups. These examples include six-membered, five-membered, and bicyclic heteroaryl groups, which include various heteroatoms (i.e., oxygen and sulfur as well as nitrogen). This range of species is well representative of the genus "heteroaryl", as discussed further below.

The independent claims also specify that the solvent is a noncomplexing solvent, as stated at page 11, line 26 of the specification. Dependent claims 59 and 61 specify that the solvent is selected from ethers, hydrocarbons, and mixtures thereof; dependent claims 60 and 62 specify that the solvent is selected from THF, toluene, and mixtures thereof. Support is found, for example, at page 11, lines 26-31 of the specification.

No new matter is added by any of the amendments.

II. Rejections under 35 U.S.C. §112, First Paragraph

Claims 17 and 57 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and use the invention without undue experimentation. Specifically, the Examiner objected to the description of the heterocyclic binding groups in these claims.

As noted above, claims 17 and 57 have been amended to incorporate the subject matter of claim 23; that is, to state that the binding group Cy_N is a heteroaryl group. Support is found in original claim 23 and in the specification at page 4, line 6.

In the specification and the enclosed Declaration under 37 CFR §1.132, six examples of N-heterocyclic aromatic rings are shown to be effective as binding groups in the subject catalysts. The specification shows 2-pyridyl (e.g. Tables 1, 2, and 3) and a bicyclic binding group, 2-quinolinyl (page 15,

lines 17-20). The enclosed Declaration illustrates reactions in which the binding groups are 2,5-dimethyloxazole, oxazole, and 2,5-dimethylthiazole. These examples include five-membered, six-membered, and bicyclic heteroaryl groups, which include various heteroatoms (i.e., oxygen and sulfur as well as nitrogen) and are both substituted and unsubstituted. This range of species is well representative of the genus "heteroaryl" as claimed. Further, the aromaticity of the groups ensures that they are chemically and conformationally stable. Based on these known properties and the range of groups demonstrated to be effective, one of skill in the art would have a reasonable expectation of success from the use of N-heteroaryl binding groups, as claimed, in general.

In view of the foregoing, the applicants request that the rejections under 35 U.S.C. §112, first paragraph be withdrawn.

III. Rejections under 35 U.S.C. §112, Second Paragraph

Claims 17, 20-23 and 55 (57) were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner states that the claims are "ambiguous claiming any nonprotic solvents" and "any 5-7 membered ring with 1-6 carbon ring atoms, with remaining ring atoms being oxygen or nitrogen".

This rejection is respectfully traversed for the following reasons. (Applicants note that claims 22 and 23 have been cancelled.)

With respect to the heterocyclic binding groups, the claims have been amended, as discussed above, to recite that the binding group is an N-heteroaryl group. Nitrogen-containing heteroaryl groups are known to those of skill in the art, and a skilled person would readily know whether a given binding group met the language of the claims. Further, the term "heteroaryl" will not encompass unstable structures, as noted above in the discussion of enablement.

With respect to the solvent, the applicants note that the term "nonprotic" is not in fact "ambiguous" (that is, of uncertain meaning or having more than one meaning). One of skill in the art would clearly know whether or not a given solvent is "nonprotic". The Examiner's objections, particularly the remarks in the Office action of July 14, 2000, seem to be directed more to the scope of the term than the clarity of the term.

The specification teaches characteristics and examples of preferred solvents at page 11, lines 6-7 and 26-28:

> The ligand L^1 and starting complex are stirred in an inert, nonprotic solvent such as THF or toluene...

All of these operations are carried out in a suitable aprotic and non-complexing solvent, such as, for example, THF, ether, toluene, other hydrocarbon solvents, chlorinated solvents, or a mixture thereof...

The independent claims have been amended to specify that the solvent is "non-complexing". The claims thus exclude the use of solvents that could complex with the metal atoms in the subject catalysts, such as, for example, acetonitrile.

The applicants submit that selection of a suitable nonprotic, noncomplexing solvent for contacting the chiral ligand and heteracoordinate metal complex, given the guidance above, is a procedural variation well within the ability of a skilled practitioner, and would not constitute undue experimentation. The Court has held that claims cannot be rejected under 35 U.S.C. §112 "for noninclusion of limitations dealing with factors which must be presumed to be within the level of ordinary skill in the art." *In re Skrivan*, 166 USPQ 85 (CCPA, 1970).

In addition, the claims also include the limitation that the "complex undergoes a ligand exchange reaction, such that L^1 becomes coordinated to said metal", thus producing a catalytic composition which is "effective to catalyze the enantioselective alkylation of an allyl group bearing a leaving group at its allylic position". Accordingly, solvents in which this ligand exchange reaction does not occur, or which produce a product which is ineffective to catalyze the enantioselective alkylation as recited, would not fall within the scope of the claims. Nor would it require undue experimentation for a skilled person to determine if a selected nonprotic solvent were effective in this regard. This could be done by determining the composition of the reaction product and/or its activity in catalyzing the asymmetric alkylations described in the specification, according to known procedures, including those described in the specification.

The applicants also submit that it would be unduly limiting to restrict the claims to solvents used in the Examples, e.g. THF and/or toluene. Such claims could be circumvented by the use of a similar solvent falling within the scope of the broader claims, e.g. tetrahydropyran, benzene, or xylene, thus denying the applicants the fair benefit of their discovery.

In view of the foregoing, the applicants respectfully request that the Examiner withdraw the rejections under 35 U.S.C. §112, second paragraph.

IV. Rejections under 35 U.S.C. §103

Claims 17-23 and 53-56 were rejected under 35 U.S.C. §103(a) as being unpatentable over:

(1) Trost and Merlic, *JACS* **112**:9590 (1990)

(2) Trost and Lautens, *Tetrahedron* **43**(21):4817 (1987)

(3) Trost and Lautens, *JACS* **109**:1469 (1987) and

(4) Trost and Murphy, *Organometallics* **4**(6):1143 (1985).

The rejection was reiterated verbatim from the Office Action of July 14, 2000, with no comment on the applicants' response of October 16, 2000. The rejection is respectfully traversed in light of the following remarks.

A. The Invention

The applicants' invention, as embodied in claim 17, is directed to a catalytic composition which is useful in catalyzing enantioselective allylic alkylations. The composition is formed by contacting, in a nonprotic solvent, a hexacoordinate complex of a metal selected from W(0), Cr(0), and Mo(0) with a chiral ligand. The chiral ligand includes a chiral component (i), as recited in claim 17 above, linked to N-heteroaryl binding groups (ii). Alternatively, the chiral component can be an axially chiral 1,1'-binaphthyl system (claim 57), also linked to N-heteroaryl binding groups. Each such binding group has a ring nitrogen atom effective to bind to the metal atom, and is linked to the chiral component at a ring carbon adjacent to the binding ring nitrogen atom.

As shown in the specification, the claimed compositions are effective to catalyze allylic alkylation with high enantioselectivity, routinely giving values of % e.e. in the high 80's and 90's and frequently up to 99% e.e. The catalysts also give a high rate of reaction and are effective with a wide variety of substrates, as noted in the specification at page 26, lines 7-10.

B. The Prior Art

(1) Trost and Merlic, *JACS* **112**:9590 (1990)
(2) Trost and Lautens, *Tetrahedron* **43**(21):4817 (1987)
(3) Trost and Lautens, *JACS* **109**:1469 (1987)

These references were discussed in the previous response. To reiterate and summarize, they discuss reactivity, chemoselectivity, regioselectivity, and/or stereospecificity (i.e. inversion vs. retention) in molybdenum complex-catalyzed allylic alkylations. Ligands in these complexes include CO, CH_3CN, bipyridyl, and bis-phosphines. None of these references disclose chiral ligands of any kind; nor do they address enantioselectivity.

(The Office Action states that molybdenum-isonitrile complexes, shown in reference (1), are "a limitation of claim 19". However, claim 19 recites complexes that may be used as starting materials in forming the catalysts of the invention, not the catalysts themselves.)

(4) Trost and Murphy, *Organometallics* **4**(6):1143 (1985)

This reference describes enantioselective allylic alkylations using a palladium complex having chiral

ligands which include binaphthyl phosphine- (**6**) and binaphthyl phosphinate-based ligands (**7** and **11**). The maximum e.e. reported with these complexes was 69%. In none of these ligands is the chiral component (i.e. the binaphthol moiety) linked to a heteroaryl binding group having a binding ring nitrogen atom, as presently claimed. Nor does the reference describe molybdenum, tungsten or chromium complexes.

C. Analysis

In order to establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references or in knowledge generally available to one skilled in the art, to modify a reference or combine reference teachings. The prior art must also provide a reasonable expectation of success. Finally, the prior art reference, or references when combined, must teach or suggest all the claim limitations. (MPEP §2143; emphasis added.)

Of the four references cited, three of them disclose no chiral ligands whatsoever, nor do they address enantioselective reactions. The reference that does employ chiral ligands (reference (4)) employs a palladium complex having chiral ligands in which the binding moiety is a phosphorus atom, as noted above. None of the references teaches or suggests the chiral ligand as claimed. Therefore, a *prima facie* case of obviousness has not been established.

The applicants therefore request that the rejections under 35 U.S.C. §103(a) be withdrawn.

V. Conclusion

In view of the foregoing, the applicant submits that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 324-0880.

No further fees are believed necessary with this communication. However, the Commissioner is hereby authorized and requested to charge any deficiency in fees herein, or credit any overpayment, to Deposit Account No. 04-0531.

Respectfully submitted,

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Amendments to specification filed May 11, 2001
Atty. Docket No. 8103-0190.20

Second paragraph, page 1:

This invention was made with government support under contract 5R37 GM13598-30 awarded by the National Institutes of Health and under contract CHE-9510472 awarded by the National Science Foundation. Accordingly, the United States Government has certain rights in this invention.

Amendments to claims filed May 11, 2001
Atty. Docket No. 8603-0190.20

17. (Three times amended) A catalytic organometallic composition, wherein the composition is the product of a process which comprises contacting, in a nonprotic, noncomplexing solvent,

(a) a chiral ligand L^1 comprising:

(i) a chiral component derived from a chiral diamine, diol, or amino alcohol, said component having first and second chiral centers, each substituted with a group X selected from -O- or -NR-, where R is hydrogen or lower alkyl,

wherein said chiral centers are connected by a direct bond or by a chain of one to three atoms comprising linkages selected from alkyl (carbon-carbon), alkyl ether (carbon-oxygen), alkyl amino (carbon-nitrogen), or a combination thereof,

and, linked to each said group X,

(ii) a [heterocyclic] heteroaryl binding group Cy_N [comprising a 5- to 7- membered ring having 1 to 6 carbon ring atoms, with the remaining ring atoms selected from oxygen and nitrogen, and] having a ring nitrogen atom effective to bind to a metal atom selected from the group consisting of molybdenum, tungsten, and chromium,

wherein said [heterocyclic] binding group is linked to said group X at a ring carbon adjacent to said ring nitrogen atom, is optionally substituted with one or more groups selected from alkyl, alkenyl, aryl, aralkyl, alkoxy, aryloxy, acyl, acyloxy, amide, tertiary amine, nitro, or halogen, and may be fused to one or more additional rings,

with

(b) a hexacoordinate complex of a metal selected from tungsten(0), chromium(0), and molybdenum(0),

whereby said complex undergoes a ligand exchange reaction, such that L^1 becomes coordinated to said metal;

wherein said composition is effective to catalyze the enantioselective alkylation of an allyl group bearing a leaving group at its allylic position.

56. (Amended) The composition of claim 17 [55], wherein said ligand L_l has the structure

$$Cy_N–(C=O)–X–C^*R^1R^3–C^*R^2R^4–X–(C=O)–Cy_N$$

wherein said chiral centers are connected by a direct bond, R^1 and R^2 are as defined above, R^3 and R^4 are hydrogen, and binding groups Cy_N are as defined above.

57. (Twice Amended) A catalytic organometallic composition, wherein the composition is the

product of a process which comprises

contacting, in a nonprotic, noncomplexing solvent, a chiral ligand L^1 comprising:

(a) an axially chiral 1,1'-binaphthyl system, said system substituted at its 2 position and at its 2' position with a group X selected from -O- or -NR-, where R is hydrogen or lower alkyl, and, linked to each said group X,

(ii) a [heterocyclic] heteroaryl binding group Cy_N [comprising a 5- to 7- membered ring having 1 to 6 carbon ring atoms, with the remaining ring atoms selected from oxygen and nitrogen, and] having a ring nitrogen atom effective to bind to a metal atom selected from the group consisting of molybdenum, tungsten, and chromium,

wherein said [heterocyclic] binding group is linked to said group X at a ring carbon adjacent to said ring nitrogen atom, is optionally substituted with one or more groups selected from alkyl, alkenyl, aryl, aralkyl, alkoxy, aryloxy, acyl, acyloxy, amide, tertiary amine, nitro, or halogen, and may be fused to an one or more additional rings;

with a hexacoordinate complex of a metal selected from tungsten (0), chromium (0), and molybdenum(0),

whereby said complex undergoes a ligand exchange reaction, such that L^1 becomes coordinated to said metal;

wherein said composition is effective to catalyze the enantioselective alkylation of an allyl group bearing a leaving group at its allylic position.

59. (New) The composition of claim 17, wherein said solvent is selected from the group consisting of ethers, hydrocarbon solvents, and mixtures thereof.

60. (New) The composition of claim 59, wherein said solvent is selected from the group consisting of THF, toluene, and mixtures thereof.

61. (New) The composition of claim 57, wherein said solvent is selected from the group consisting of ethers, hydrocarbon solvents, and mixtures thereof.

62. (New) The composition of claim 61, wherein said solvent is selected from the group consisting of THF, toluene, and mixtures thereof.